6) A marked up copy of the specification;

7) Letter to Draftsperson with Formal Figures; and,

8) A receipt indication postcard.

AMENDMENT

Please amend the specification and claims as follows.

In the Specification.

Delete the paragraph at page 15, lines 13-15 and insert the following:

Figures 6A-6F illustrate the use of the *blm* NRPS and PKS enzymes to synthesize a variety of hybrid polyketide/peptide molecules including, but not limited to, a family of oxazolines/oxazoles, and thiazoline/thiazoles. Figure 6A synthesis using BlmIX, BlmVIII, and BlmVII. Figure 6B synthesis using NRPS, BlmVIII, and BlmVII. Figure 6C synthesis using BlmIX, BlmVIII, and BlmVII. Figure 6D synthesis using BlmIX, BlmVIII, and NRPS (C, A^N, PCP). Figure 6E synthesis using BlmIX, BlmVIII and NRPS (C, A^C, PCP). Figure 6F synthesis using BlmIX, BlmVIII, and NRPS (C, A^C, PCP, OX).

Delete the paragraph at page 19, lines 12-19 and insert the following:

The nucleic acids comprising the *blm* gene cluster are identified in Tables I and II and listed in the sequence listing provided herein (SEQ ID NOS: 1 and 2, GenBank Accession number AF210249 (which replaces sequence AF149091), and SEQ ID NO:3, GenBank Accession number AF210311). In particular, Table I identifies genes and functions of open reading frames (ORFs) responsible for the biosynthesis of the hybrid peptide/polyketide/peptide backbone and sugar moieties of bleomycin, while Table II identifies a number of ORFs comprising the *blm* gene cluster, identifies the activity of the catalytic domain encoded by the ORF and provides primers for the amplification and isolation of that orf.

Delete the Table 1 at pages 19-20 and insert the following:

Table I. Determined functions of ORFs in the bleomycin biosynthesis gene cluster

Gene	Amino acids	Sequence Homolog[1]	Proposed function[2, 3]
orf8	424 SEQ ID NO: 115	YqeR (BAA12461)	Oxidase

orf9 (blmC)	498 SEQ ID NO: 114	RfaE (AAD07904)	NDP-glucose synthase
orf10 (blmI)	90 SEQ ID NO: 113	GrsB (P14688)	Type II PCP
orf11 (blmD)	545 SEQ ID NO: 112	NodU (Q53515	Carbamoyl transferase
orf12 (blmE)	390 SEQ ID NO: 111	RfaF (AAD16056)	Glycosyl transferase
orf13	187 SEQ ID NO: 110	MbtH (O05821)	Unknown
orf14 (blmII)	462 SEQ ID NO: 109	Nrp (CAA98937)	NRPS condensation enzyme
orf15	339 SEQ ID NO: 108	SyrP (1890776)	Regulation
orf16 (blmIII)	935 SEQ ID NO: 107	HMWP2 (P48633), McbC (P23185)	A PCP Ox
orf17 (blmIV)	2626 SEQ ID NO: 106	HMWP2 (P48633)	C A PCP Cy A PCP Cy
orf18	638 SEQ ID NO: 105	AsnB (2293165)	Asparagine synthetase
orf19 (blmF)	494 SEQ ID NO: 104	RfbC (Q50864)/BlmOrf1 (507319)	Glycosyl transferase/β-hydroxylase
orf20 (blmG)	325 SEQ ID NO: 103	YtcB (2293288)	Sugar epimerase
orf21 (blmV)	645 SEQ ID NO: 102	McyB (2708278)	PCP C
orf22 (blmVI)	2675 SEQ ID NO: 101	ACoAS (1658531), PksD (S73014) SnbDE (CAA67249)	A^4 ACP C A PCP C A
orf23 (blmVII)	1218 SEQ ID NO: 100	SyrE (3510629)	C A PCP
orf24 (blmVIII)	1841 SEQ ID NO: 99	HMWP1 (CAA73127)	KS AT MT KR ACP
orf25 (blmIX)	1066 SEQ ID NO: 98	SafB (1171128)	C A PCP
orf26 (blmX)	2162 SEQ ID NO: 97	TycC (2623773)	C A PCP C A PCP
orf27 (blmXI)	688 SEQ ID NO: 96	SyrE (3510629)	NRPS condensation enzyme
orf28	239 SEQ ID NO: 95	SC9C7.04C (CAA22716)	Unknown
orf29	582 SEQ ID NO: 94	YvdB (CAB08068)	Transmembrane transporter
orf30	113 SEQ ID NO: 93	SmtB (P30340)	Regulation
orf31	117 SEQ ID NO: 116	PhnA (P16680)	Unknown

Delete Table II at pages 21-23 and insert the following replacement Table II:

Table II. *Blm* gene cluster open reading frames (ORFs) and primers for ORF amplification.

Orf #	Activity	Method	Primers Forward Reverse	Seq ID No.
orf-8 SEQ ID NO:115	Oxygen-independent coproporphyrinogen III oxidase	Gapped-blast comparison[1]	F: ATGAGCCACGCCATCGGA R: TCAGGCGCGTTCGGGGGC	5 6
orf-9 SEQ ID NO:114	ADP-heptose synthase (*blmC*)	Gapped-blast comparison[1]	F: GTGAACACCGACCTGCCC R: TCATGGGGTGTCTCCCTC	7 8
orf-10 SEQ ID NO:113	Peptidyl carrier protein (*blmI*)	Expression and biochemical characterization.[2]	F: ATGAGCGCCCCGCGGGGC R: TCACCGGTCCCGCTCCCC	9 10
orf-11 SEQ ID NO:112	Carbamyltransferase (*blmD*)	Gapped-blast comparison[1]	F: ATGAGCGCCGACCCGTCC R: TCATGAGCGGGCCGCCGT	11 12
orf-12 SEQ ID NO:111	ADP-heptose:LPS heptosyl transferase (*blmE*)	Gapped-blast comparison[1]	F: ATGACCACCCCCATGACC R: TCATGGGGTACTCCTGAT	13 14
orf-13 SEQ ID NO:110	Homolog of mbtH in the synthesis of mycobactin	Gapped-blast comparison[1]	F: ATGACCACGACCCCGCGG R: TCAGGTGCCGGACACGCG	15 16
orf-14 SEQ ID NO:109	Peptide synthetase (condensation, *blmII*)	Gapped-blast comparison[1]	F: GTGACCGCCCCCGGCACA R: TCATCGGTGGCTCCTCGT	17 18
orf-15 SEQ ID NO:108	Regulatory gene (homolog of *syrP*)	Gapped-blast comparison[1]	F: GTGAACCGGCACGGCCCC R: TCACGCGCTCACCTCGTC	19 20
orf-16 SEQ ID NO:107	Mutated peptide synthetase- oxidase (NRPS-0, *blmIII*)	Gapped-blast comparison[1]	F: GTGACGAGCGCCCGGCCC R: TCACGGGGCCTCCGTGCG	21 22
orf-17 SEQ ID NO:106	Peptide synthetase (NRPS-2-1,*blmIV*)	Expression and biochemical characterization.[2]	F: ATGCTGCACGGCGCCGCG R: TCACTCCGGTCCACCTCC	23 24
orf-18 SEQ ID NO:105	Asparagine synthetase	Gapped-blast comparison[1]	F: GTGAGGCCCGTGTGCGGC R: TCAGCCACCGTTGCCGCC	25 26
orf-19 SEQ ID NO:104	Homolog of hydroxylase-dehydrogenase (*blmF*)	Gapped-blast comparison[1]	F: GTGAAGGACCTCGGCCGG R: TCACTCCCCCGGTGCCGG	27 28
orf-20 SEQ ID NO:103	Nucleotide-sugar epimerase (*blmG*)	Gapped-blast comparison[1]	F: GTGACATGGACCGTGGTG R: TCAGGCATCGGCCCTCCC	29 30
orf-21 SEQ ID NO:102	Peptide synthetase (NRPS-3CT, *blmV*)	Gapped-blast comparison[1]	F: ATGCGCGGGCATGACGAC R: TCACGGTGTCTCTCCCTC	31 32
orf-22 SEQ ID NO:101	Peptide synthetase (NRPS-5-4-3, *blmVI*)	Expression and biochemical characterization.[2]	F: ATGAGCCGGCCGGCCGGC R: TCATGCTCGGTCATCGCC	33 34
orf-23 SEQ ID NO:100	Peptide synthetase (NRPS-6, *blmVII*)	Expression and biochemical characterization.[2]	F: GTGACCACGCCCCGCATC R: TCATTCGGGACGCGGGCA	35 36
orf-24 SEQ ID NO:99	Polyketide synthase (*blmVIII*)	Gapped-blast comparison[1]	F: ATGAGCCATGCCGACGCG R: TCACAGCACCACCTCTTC	37 38
orf-25 SEQ ID NO:98	Peptide synthetase (NRPS-7, *blmIX*)	Gapped-blast comparison[1]	F: ATGACCCCGGCCGCCGAC R: TCATCGTCCGCCGCCTTT	39 40
orf-26 SEQ ID NO:97	Peptide synthetase (NRPS-9-8, *blmX*)	Gapped-blast comparison[1]	F: ATGCCTCGGTGTGCCCGA R: TCATTCGGCGGCACCTCC	41 42

orf-27 SEQ ID NO:96	Peptide synthetase (condensation, *blmXI*)	Gapped-blast comparison[1]	F: GTGGGTTTCCGTCGAGCG R: TTACACCCTCCGTTTCTC	43 44
orf-28 SEQ ID NO:95	Phosphatidylserine decarboxylase	Gapped-blast comparison[1]	F: ATGGCACAGGACCTGAAC R: TCAACGCCACCGGATCTT	45 46
orf-29 SEQ ID NO:94	Transmembrane transporter	Gapped-blast comparison[1]	F: GTGAGCTCCCTCGCCGTC R: TCATCGTCGGGCACTCGG	47 48
orf-30 SEQ ID NO:93	Metal dependent regulatory element	Gapped-blast comparison[1]	F: GTGCCGGTTCCGCTGTAT R: TCACCGGGCACTGACCTC	49 50
orf-31 SEQ ID NO:116	PHNA homolog	Gapped-blast comparison[1]	F: GTGACCGAGAACCTTCCG R: TCAGACCTTCTTGACCAC	51 52
orf-32 SEQ ID NO:117	Peptide synthetase (NRPS-11-10)	Gapped-blast comparison[1]	F: ATGGCCTCAGACGCTTTG R: TCATTGAGACTCCTCCTC	53 54
orf-33 SEQ ID NO:118	Putative transporter	Gapped-blast comparison[1]	F: ATGATGAAGTCAAGCCGC R: TCAGTGGCTTACAAGGAG	55 56
orf-34 SEQ ID NO:119	Homolog of clavaminic acid synthase	Gapped-blast comparison[1]	F: ATGACTGACCTGCCGTTG R: TCACACCAGCAGCGAGGT	57 58
orf-35 SEQ ID NO:120	Thioesterase	Gapped-blast comparison[1]	F: ATGGATTTCCCCCTCACC R: TCATGCCCCTACCTCGGC	59 60
orf-36 SEQ ID NO:121	Putative transporter	Gapped-blast comparison[1]	F: ATGACCGCGCGCGTCGAC R: TCACTCCTCGGCTTCGGC	61 62
orf-37 SEQ ID NO:122	Unknown	Gapped-blast comparison[1]	F: GTGTCCAAGAACGCGGCG R: TCATCGGCTCGCCTCGTG	63 64
orf-38 SEQ ID NO:123	Peptide synthetase (NRPS-12)	Gapped-blast comparison[1]	F: ATGACCCTCACCCTGCGG R: TCACTCGGGCACTCCTTC	65 66
orf-39 SEQ ID NO:124	Regulatory gene (homolog of *SyrP*	Gapped-blast comparison[1]	F: GTGACCGGTTCCGTAACG R: TCATGAGTCCGCCGAGGT	67 68
orf-40 SEQ ID NO:125	Peptide synthetase	Gapped-blast comparison[1]	F: ATGACAGAGGTCCGAGGT R: CCCGGCAACCGCCCTCCC	69 70
orf-41 SEQ ID NO:126	4'-phosphopantetheinyl transferase (*pptA*)	Expression and biochemical characterization.[2]	F: GTGATCGCCGCCCTCCTG R: TTACGGGACGGCGGTCCG	71 72

Delete the paragraph on page 69, line 17 through page 70, line 20 and insert the following:

The sequence of the 1,761-bp *Bam*HI-*Sal*I fragment was analyzed for coding regions by using the CODONPREFERENCE and TESTCODE programs of the GCG package (Genetics Computer Group, Madison, Wisconsin). Two complete ORFs (*pptA, orf3*) and two incomplete ORFs (*orf1, orf4*) were identified within the sequenced region (Figure 13). The first ORF from left to right (designated *orf1*) starts out of the analyzed area and ends with a TGA codon at position 248 of the sequenced fragment. Comparison of the deduced product of *orf1* with proteins encoded by nucleic acids in databases showed similarities with Rv2795c from *Mycobacterium tuberculosis* (GenBank AL008967) and SC5A7. 22 from *S. coelicolor* (GenBank AL031107), both of unknown function. The second ORF, *pptA*, contains the sequence amplified by PCR and used for the cloning of this locus. It comprises 741 nucleotides, starting with a GTG codon (position 245) which is

coupled to the stop codon of *orf1*, and ending with a TAA codon. The starting codon of *pptA* is preceded by a potential ribosomal binding site (RBS), GGGAG. The overall (76. 6%) and third codon position (93. 9%) G+C contents and the codon usage of *pptA* are similar to those found in other *Streptomyces* genes, with the exception of the stop codon (TAA), which is most uncommon in this group of organisms (Wright et al. *Gene* (1992) 113:55-65). The *pptA* gene encodes a protein of 246 amino acids with a predicted molecular mass of 25,619 Da and a pI of 4. 76, which contains the conserved PPTase motifs. Databases searches with PptA showed significant similarities to the putative actinomycete PPTases (39-52%/48-61% identity/similarity) and to confirmed bacterial PPTases such as EntD from *E. coli* (17%/24% identity/similarity) (Lambalot et al. *Chem. Biol.* (1996) 3:923-936). The third ORF, *orf3*, is separated from *pptA* by an apparently noncoding DNA region of 153 bp, and it is transcribed in opposite and convergent direction with respect to *orf1-pptA*. The gene *orf3* comprises 240 nucleotides, starting with an ATG codon (position 1358) and ending with TGA. The starting codon of *orf3* is preceded by the sequence GAAGG, a potential RBS. The deduced product of *orf3* encodes a protein of 79 amino acids with a predicted mass of 7,555 Da and a pI of 7. 17. The Orf3 protein shows similarities to the N-terminal region of SC5H1. 35c, a protein of unknown function from *S. coelicolor* (encoded by nucleic acid sequence in GenBank AL049863). Analysis of Orf3 with the SignalP program (Nielsen et al. *Protein Engineer.* (1997) 10:1-6) predicts an N-terminal signal peptide which would be cleaved between residues 27 and 28 (ALA-DS), suggesting that the mature protein (52 amino acids, 5,099 Da, pI 4. 31) would be secreted. Between *orf3* and *orf4* there is an apparently noncoding region of 251 nucleotides. The *orf4* gene is transcribed in opposite and divergent direction with respect to *orf3*. It starts with an ATG codon at position 1610, preceded by a potential RBS (GGAGG), and ends out of the sequenced fragment. The deduced protein product (50 amino acids) of the incomplete *orf4* contains a potential NAD/FAD binding motif, $GXGX_2GX_3GX_6G$ (SEQ ID NO:92) (Scrutton et al. *Nature* (1990) 343:38-43), showing low similarities to diverse oxidoreductases.

In accordance with 37 CFR §1.121 a marked up version of the above-amended paragraph(s) illustrating the changes introduced by the forgoing amendment(s) are provided in Appendix C.